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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/020,063 | 12/13/2001 | Kevin P. Baker | GNE.2830P1C65 | 9309 |

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| EXAMINER | |
|---|---|
| BUNNER, BRIDGET E | |
| ART UNIT | PAPER NUMBER |
| 1647 | |

DATE MAILED: 04/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/020,063 | BAKER ET AL. | |
| | Examiner | Art Unit | |
| | Bridget E. Bunner | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *33,38-40 and 44-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33,38-40 and 44-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/3/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application, Amendments and/or Claims*

The amendment of 03 February 2005 has been entered in full. Claims 33, 38-40, 44, and 46-47 are amended.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 33, 38-40 and 44-47 are under consideration in the instant application.

### *Withdrawn Objections and/or Rejections*

1. The objections to the specification at pg 2 of the previous Office Action (20 December 2004) are *withdrawn* in view of the amended specification and title (03 February 2005).

2. The rejections to claims 28-33, 36-37, and 41-47 under 35 U.S.C. 112, second paragraph, as set forth at pg 17-18 of the previous Office Action (20 December 2004) are *withdrawn* in view of the amended claims and cancelled claims (03 February 2005).

3. The rejections to claims 28-47 under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph (enablement) as set forth at pg 2-14 of the previous Office Action (20 December 2004) are *withdrawn in part* in view of cancelled and amended claims (03 February 2005). Please see section on 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, below.

4. The rejection to claims 28-33, 36-37, and 41-47 under 35 U.S.C. § 112, first paragraph (written description) as set forth at pg 14-17 of the previous Office Action (20 December 2004) is *withdrawn* in view of the amended and cancelled claims (05 February 2005).

5. The rejection to claims 28-30 and 41-47 under 35 U.S.C. § 102(e) as set forth at pg 18-19 of the previous Office Action (20 December 2004) is *withdrawn* in view of the amended and cancelled claims (03 February 2005).

6. The supplemental information disclosure statement filed on 03 February 2005 has been considered.

***New Claim Objections***

7. Claims 33 and 38 are objected to because of the following informalities:

7a. In claim 33, line 2 (part (a)), the phrase "shown in" must be deleted.

7b. Claim 38 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 38 recites the isolated nucleic acid of claim 33 comprising the nucleic acid sequence of SEQ ID NO: 373. However, claim 33 also recites an isolated nucleic acid comprising the nucleic acid sequence of SEQ ID NO 373.

Appropriate correction is required.

***Claim Rejections - 35 USC § 101 and 35 USC § 112, first paragraph***

8. Claims 33, 38-40, and 44-47 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation. The basis for this rejection is set forth for claims 28-47 at pg 2-8 of the previous Office Action (20 December 2004).

Specifically, claims 33, 38-40, and 44-47 are directed to an isolated nucleic acid comprising the nucleic acid sequence of SEQ ID NO: 373. The claims also recite an isolated nucleic acid comprising the full-length coding sequence of the nucleic acid of SEQ ID NO: 373. The claims recite an isolated nucleic acid comprising the full-length coding sequence of the cDNA deposited under ATCC accession number 203465. The claims also recite a vector and host cell.

Applicant's arguments (03 February 2005), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that the results presented in the instant specification have utility for the PRO1759 polynucleotide and polypeptide (SEQ ID NOs: 373 and 374, respectively). Applicant argues that the utilities of PRO1759 polynucleotide include the use as a diagnostic tool, as well as therapeutically as a target for treatment, based on the data that PRO1759 cDNA is more highly expressed in lung tumor and colon tumor tissue compared to normal lung and colon tissue. Applicant states that the specification discloses that the nucleic acids encoding PRO1759 has a $\Delta$Ct value of >1.0, which is more than 2-fold increase, in at least 3 of the tumors listed in Table 8.

Applicant's arguments have been fully considered but are not found to be persuasive. In the instant case, the specification provides data showing that polynucleotides encoding PRO1759 are more highly expressed in lung and colon tumor tissue as compared to normal lung and colon tissue. However, there is no further supporting evidence to indicate that the polypeptide encoded by the polynucleotide of the instant invention is also differentially expressed in the tumor tissue as compared to the normal tissue and as such, one of skill in the art would conclude that is it not

supported by a substantial asserted utility or a well-established utility. Utility of a novel nucleic acid presumably involved in cancer will depend on the role that the expressed polypeptide plays in cancer initiation, progression, growth, maintenance, etc.

Furthermore, as discussed by Haynes et al (1998, Electrophoresis, 19: 1862-1871), polypeptide levels cannot be accurately predicted from mRNA levels, and that, according to their results, the ratio varies from zero to 50-fold (page 1863). The literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (Journal of Proteome Research 2: 405-412, 2003) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (pg 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). Similarly, Chen et al. (2002, Molecular and Cellular Proteomics 1: 304-313) disclose that twenty-eight of the 165 protein blots (17%) or 21 of 98 genes (21.4%) had a statistically significant correlation between protein and mRNA expression (see Abstract and Table I). In addition, their results showed that no significant correlation between mRNA and protein expression was found ($r = -0.025$), if the average levels of mRNA or protein among all samples were applied across the 165 protein blots (98 genes). The reference also teaches that the mRNA/protein correlation coefficient varied among proteins with multiple isoforms, indicating potentially separate isoform-specific mechanisms for the regulation of

protein abundance. In this study using a quantitative analysis of mRNA and protein expression within the same lung adenocarcinomas, it is showed that only a minority subset of the proteins exhibited a significant positive correlation with mRNA abundance.

Given the small increase in DNA copy number of PRO1759, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA or polypeptide levels. Further research needs to be done to determine whether the small increase in PRO1759 DNA supports a role for the peptide in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and,
>
> "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the specification's assertions that the PRO1759 polynucleotides encoding the polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

Furthermore, the declarations of Dr. Goddard and Dr. Askenazi, as relied upon in Applicant's arguments (03 February 2005), have not been considered by the Examiner because they were not submitted with the Response of 03 February 2005. However, even if the declarations were submitted under 37 CFR § 1.132, they would be insufficient to overcome the rejection of claims 28-35 and 38-40, based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office Action (20 December 2004).

Specifically, at page 9 of the response of 03 February 2005, Applicant discusses the accuracy of the Taq DNA polymerase assay, stating that the Taqman PCR technique is sensitive enough to detect at least a 2-fold increase in gene copy number (paragraph 1) and that this increase is significant and useful. Applicant directs the Examiner to page 3 of the Dr. Goddard declaration that describes the gene amplification technique in the present application and references that attest to the use of this technique in diagnostic and prognostic fashion. This argument has been fully considered but is not deemed persuasive because it evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO1759 gene has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO1759 nucleic acid was amplified in two cancer samples, to a minor degree (about 2.5 fold). No mutation or translocation of PRO1759 has been associated with any type of cancer versus normal tissue. It is not known whether PRO1759 is expressed in corresponding normal tissues, and what the relative levels of expression are. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO1759 is amplified in a variety of samples and invites the artisan to determine the significance of this increase. One

cannot determine from the data in the specification whether the observed "amplification" of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an increase in transcription rates. It remains that, as evidenced by Haynes et al., Hu et al., and Chen et al., the issue is simply not predictable, and the specification presents a mere invitation to experiment.

Furthermore, Applicant's arguments do not provide data such that the examiner can independently draw conclusions. It is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, as discussed above, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (pg 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). The instant specification also does not demonstrate that the increased copy number of PRO1759 DNA in human lung tumors and colon tumors leads to an increased expression of PRO1759 polypeptide in these tumors. Therefore, since Applicants does not provide information regarding the level of expression, an activity, or a role in cancer or any other disease for the PRO1759 polypeptide, the polynucleotide and polypeptide lack a substantial utility or well established utility.

Applicant also contends that the claimed polynucleotide encoding the PRO1759 polypeptide would have diagnostic utility even if there is no positive correlation between gene

expression and expression of the encoded polypeptide. Further, it is asserted that even if there was no correlation between gene expression and increased or decreased protein expression for PRO1759, the gene that is over-expressed or under expressed in cancer would still have credible, specific and substantial utility. Applicant asserts that this position is supported by the declaration by staff scientist Ashkenazi. It claims that the purpose of the experiments that measured increases in gene copy number was to identify tumor cell markers useful for cancer treatment and to identify cancers for which there was an absence of gene product over-expression. The Ashkenazi declaration further argues that, even when amplification of a gene in a tumor does not correlate with an increase in polypeptide expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment. The examiner agrees that evidence regarding lack of over-expression would also be useful. However, there is no evidence as to whether the gene products (such as the PRO1759 polypeptide) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not substantial.

Finally, Applicant asserts that the teachings of Hittelman et al. suggest that the chronic exposure to carcinogens leads to outgrowth of abnormal clones associated with chromosomal instability. Applicant contends that Hittelman et al. shows that an increase in chromosome number is a common characteristic of cancerous and pre-cancerous epithelial cells and therefore, increase in chromosome number or gene amplification is useful as a marker for a cancerous or pre-cancerous state. Applicant argues that whether a pre-cancerous or tumor sample were analyzed, the showing of DNA amplification of PRO1759 gene would still be significant since it would lead to the diagnosis of either a pre-cancerous state or a cancerous state. Applicant's

arguments have been fully considered but are not found to be persuasive. Specifically, a slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Because aneuploid DNA can be found in normal tissue or cells (see Fleischhacker et al. and Hittelman et al.), detection of increased DNA copy number does not necessary mean those cells containing the DNA are cancerous. The gene amplification assay disclosed in the instant specification does not provide a comparison between the lung or colon tumor samples and normal lung or colon epithelium control, and thus it is not clear that PRO1759 is amplified in cancerous lung or colon epithelium more than in damaged (non-cancerous) lung or colon epithelium. Thus, one skilled in the art would not conclude that PRO1759 is a diagnostic probe for lung or colon cancer.

9. Claims 33, 38-40, and 45-47 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The basis for this rejection is set forth for claims 28-47 at pg 9 of the previous Office Action (20 December 2004).

Applicant states that a specific and substantial asserted utility has been disclosed, as described above. Specifically, since Applicant has not provided evidence to demonstrate that the PRO1759 polynucleotide and polypeptide have a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. It is noted that the instant specification is required to teach one skilled in the art how to make and use the polypeptide encoded by the claimed polynucleotides.

***Conclusion***

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

BEB
Art Unit 1647
19 April 2005

ELIZABETH KEMMERER
PRIMARY EXAMINER